



Elsevier has created a [Monkeypox Information Center](#) in response to the declared public health emergency of international concern, with free information in English on the monkeypox virus. The Monkeypox Information Center is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its monkeypox related research that is available on the Monkeypox Information Center - including this research content - immediately available in publicly funded repositories, with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the Monkeypox Information Center remains active.

Monkeypox: An epidemiologic and clinical comparison of African and US disease

Tanya A. Sale, MD,^a John W. Melski, MD,^b and Erik J. Stratman, MD^b
Saint Paul, Minnesota, and Marshfield, Wisconsin

Monkeypox is a double-stranded DNA virus and a member of the genus *Orthopoxvirus*. Human monkeypox was first identified in the Democratic Republic of the Congo (formerly Zaire) in 1970. The first outbreak in the western hemisphere occurred in the spring of 2003. Important epidemiologic and clinical differences exist between human monkeypox in the United States and in Africa, including sex distribution, case fatality, morphology of skin lesions, and associated lymphadenopathy. These divergent clinical presentations could be caused by mode of transmission (skin inoculation vs ingestion), the skin color of affected patients, the training backgrounds of those who saw and documented disease outbreaks, the virulence of monkeypox strains involved, nutritional status, access to advanced medical care, and the prevalence of prior smallpox vaccinations. (J Am Acad Dermatol 2006;55:478-81.)

"OUT OF AFRICA, THERE IS ALWAYS SOMETHING NEW"¹
("Ex Africa semper aliquid novum")

The genera of poxviruses known to affect human beings include *Orthopoxvirus*, *Parapoxvirus*, *Yatapoxvirus*, and *Molluscipoxvirus*.² Monkeypox, a double-stranded DNA virus, is a member of the genus *Orthopoxvirus* that is known to cause human disease, along with variola virus, vaccinia virus, and cowpox virus. Much attention was initially paid to human monkeypox in Africa because of its clinical similarities to smallpox and the efforts of the World Health Organization's smallpox eradication program. More recent attention was given to human monkeypox because of an outbreak in the midwestern United States, the first such detected outbreak in the western hemisphere.³

Monkeypox virus was first identified as the causal agent of a pox infection in captive cynomolgus monkeys (*Macaca fascicularis*) in Copenhagen, Denmark, in 1959.⁴ Eight more outbreaks occurred during the next 10 years in the United States and the Netherlands among groups of captive monkeys imported from Malaysia, India, and the Philippines.⁵ Although monkeypox virus was recovered from

captive primates originally collected from these Asian areas, there is no virologic, serologic, or epidemiologic evidence that the virus occurs naturally anywhere outside of Africa.⁶ Although the definitive natural reservoir is still unknown, studies point to rope squirrels of the African genus, *Funisciurus*. Primates, rabbits, and several rodent species are also vulnerable to infection.

Human monkeypox was first identified in the Democratic Republic of the Congo (formerly Zaire) in 1970 in a 9-month-old infant initially believed to have smallpox.⁷ Human disease in central and western Africa is acquired primarily through direct animal-to-human contact. It is also transmitted from human-to-human by respiratory droplets or body fluids.⁸

INTO THE NEW WORLD

Documented human monkeypox arrived in the United States in May 2003, occurring in a 3-year-old girl from central Wisconsin. Trace-back investigations have implicated a shipment of 800 small animals from Ghana to Texas as the probable means of penetration of monkeypox virus into the United States. A sick Gambian giant-pouched rat (*Cricetomys gambianus*) from this shipment was subsequently sold to an Illinois animal vendor where it was kept in close proximity to prairie dogs (a native North American rodent [*Cynomys* species]). Prairie dogs that became infected were sold to a second animal distributor, and eventually to two pet shops and at a pet swap meet in northern Wisconsin. Additional animals from the Texas shipment, including dormice and rope squirrels, tested positive for monkeypox virus.⁹ As of July 2003, 72 cases of

From the Departments of Dermatology at Aspen Medical Group, Saint Paul,^a and Marshfield Clinic.^b

Funding sources: None.

Conflicts of interest: None identified.

Reprint requests: John W. Melski, MD, Department of Dermatology, Marshfield Clinic, 1000 N Oak Ave, Marshfield, WI 54449.
E-mail: melski.john@marshfieldclinic.org.

0190-9622/\$32.00

© 2006 by the American Academy of Dermatology, Inc.

doi:10.1016/j.jaad.2006.05.061

human monkeypox were under investigation in Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin with 37 cases confirmed through laboratory analysis.¹⁰

The Centers for Disease Control and Prevention and the Food and Drug Administration issued a joint order on June 2003 prohibiting importation of any African rodent, and the sale, transport, or release into the wild of prairie dogs, tree squirrels, sun squirrels, rope squirrels, dormice, Gambian giant-pouched rats, brush-tailed porcupines, or striped mice. The joint order was replaced by an interim final rule on November 4, 2003, that maintained the previous bans on importation, sale, transport, or release into the wild.¹¹

DIVERGENT PRESENTATIONS

Notable clinical differences exist between human monkeypox in the United States and in Africa. More than 80% of cases of human monkeypox in Africa occur in children younger than 10 years. It is mainly a disease of rural populations, with 90% of those infected inhabiting villages of less than 1000 persons.¹² Most patients are male. African monkeypox most commonly develops through contact with infected small mammals obtained for food, sport, or other reasons (72%). Spread by human-to-human contact occurs not infrequently (28%).¹³ The secondary attack rate is 3.3% to 10% among all susceptible contacts, significantly lower than smallpox's rate of 25% to 40% among unvaccinated individuals.¹⁴ Vaccination with vaccinia virus provides approximately 85% protection against monkeypox,¹⁵ although possibly less after many decades.¹⁶ An increased incidence of human monkeypox was seen in Africa from 1996 to 1999, probably because of termination of vaccinia vaccination after smallpox eradication. No evidence for increased transmissibility or relation to HIV infection was found.¹⁷ Case fatality ranges from 10% to 17%.^{13,18,19}

All human cases in the United States had direct contact with infected exotic or wild mammalian pets, and human-to-human transmission could not be confirmed. The sex ratio was approximately equal. The vast majority of patients had light skin. Of patients described in the initial outbreak, 33% had been previously vaccinated against smallpox during the era of compulsory vaccination. No case fatalities occurred.²⁰ Antiviral treatment with cidofovir or a related compound is more effective than smallpox vaccination in preventing mortality in experimental monkeypox virus infection of cynomolgus monkeys.²¹ None of the patients in the United States received these agents. Among the 9 patients hospitalized for longer than 48 hours, 5 were defined as

severely ill including one 6-year-old child who required mechanical ventilation for encephalitis.²² Adequate nutrition and supportive measures such as hydration and antibiotics may have prevented mortality in patients who were severely ill.

Human monkeypox in Africa has been well described since its initial presentation in 1970. After an incubation period of 7 to 17 days (mean 12 days), a prodrome of fever, headache, backache, and fatigue begins. This lasts for 2 to 4 days, followed by the development of skin lesions. Severity of disease ranges from mild to severe. Marked lymphadenopathy occurs in the majority of patients with submandibular, postauricular, cervical, and inguinal lymphadenopathy most commonly involved.¹⁹ In African cases, this feature was an important clinical clue that a patient was presenting with monkeypox, as compared with smallpox, which does not have such obvious lymphadenopathy.¹³

Reports in the United States describe an incubation period of 4 to 24 days (mean 14.5 days)³ followed by rash, fever, chills, lymphadenopathy, headache, sore throat, myalgias, sweats, cough, nausea, vomiting, nasal congestion, back pain, mouth sores, blepharitis, conjunctivitis, and gastrointestinal symptoms to varying degrees.^{3,19,22} Lymphadenopathy was reported in 71% of 34 confirmed cases,²² but seemed less prominent than the marked nodal involvement reported in Africa.

The most significant clinical difference between monkeypox in Africa and the United States is the morphology, evolution, and absolute number of skin lesions. Cutaneous eruptions and morphologies described in African monkeypox are much more predictable. Lesions evolve as a group from macules to papules to pustules that umbilicate, desiccate, and desquamate during a period of 14 to 21 days, often leaving residual varioliform scarring.¹⁹ Lesions measuring approximately 0.5 cm concentrate acrally and may involve mucous membranes, palms, soles, and genitals.¹⁸ The centrifugally clustered rash and pronounced lymphadenopathy help to distinguish the disease from smallpox infection. Palms and soles are involved in numerous cases.¹⁸ Inoculation lesions are not well described. In Africa, 13% of cases had less than 25 lesions, 38% had 25 to 100 lesions, and 49% had more than 100 lesions.¹⁸

In the outbreak in the United States, lesion morphology varied significantly from person to person and was even quite varied within a single family exposed to the same infectious source.²³ Infected prairie dogs had clinical manifestations similar to those exposed to monkeypox experimentally by intranasal route, namely lethargy, anorexia, vesicular lesions on the lips and tongue, and mucopurulent

nasal discharge.²⁴ In general the portal of entry to human beings was not known with certainty. However, several cases, including the index child, developed what appeared to be primary inoculation lesions surrounding bites or scratches before constitutional symptoms and widespread skin lesions. The index patient's prairie dog bite sites progressed from a red erosion to a white vesicle, then to an umbilicated pustule with a central hemorrhagic crust and satellite lesions. The index child's mother initially developed white vesicles surrounding a scratch from her pet cat on the back of her hand. Both mother and child quickly developed disseminated lesions with a haphazard distribution suggestive of hematogenous spread. These lesions, and those reported on other individuals, evolved from firm papules to vesicles to pustules, some with prominent erythematous flares. The erythematous flares noted on disseminated lesions were, in some cases, quite striking and had not been previously reported with African cases. Inoculation lesions present on the hands of both the index patient and her mother developed large hemorrhagic crusts before healing. Healing with prominent hemorrhagic crusts is also distinctive of the US cases and may correlate with a lack of complement inhibition by West African strain.²⁵ Resolution of lesions occurred after sloughing of these crusts. Most lesions left no scarring. Some lesions left minimal residual scarring, although scarring noted with the index family could be attributed solely to punch biopsy site scarring.³ Centrifugal distribution was seen in only 48% of cases with involvement of palms in 28% and soles in 9%.²² Cases described in the United States reported more than 25 lesions in 53% and more than 100 lesions in only 20% of patients.²²

DISCUSSION

The divergent clinical presentations of monkeypox in Africa and the United States could have several explanations. Cases in the United States were largely described by dermatologists who typically have an expanded descriptive nomenclature when examining skin lesions compared with other physician specialists. Differences might also be explained by the skin color of affected patients. Erythematous flares are more easily observed on lighter skin than darker skin, which could explain why flares were observed in the predominantly white patients in the United States and not in the predominantly black patients in Africa. The African male propensity may be related to increased contact through male-dominated hunting, killing, and skinning activities,²⁶ whereas US contact through pets would not be sex-specific.

It is also known through genomic sequencing that monkeypox strains belong to one of two clades (homologous groups). Monkeypox from the United States was from the less virulent West African clade rather than the more virulent Central African clade endemic in the Congo Basin.^{25,27} This may be responsible for the milder course of infection and lower mortality witnessed here. In addition, many or most African cases are likely to include ingestion of infected meat,²⁸ whereas the US cases were transmitted solely through dermal contact. This may help account for the reduced severity, earlier detection, or both in US cases. Outbreaks in Africa have also been shown to involve coinfections with varicella-zoster virus (an unrelated herpesvirus) during concomitant outbreaks of monkeypox and chickenpox.¹⁹

Finally, morbidity may have been reduced by partial herd immunity to monkeypox as a result of mandatory smallpox vaccinations that ceased in 1972 for civilians and military personnel between 1990 and 2002.²⁹ Previously unreported cases of monkeypox have been identified serologically in individuals at 13, 29, and 48 years after smallpox vaccination.¹⁶

SUMMARY

During the spring of 2003 the virus was imported into the United States by the exotic pet trade. The clinical course of human monkeypox in the United States was found to differ in a number of ways from that which had been described in Africa. This could be the result of a number of variables, including mode of transmission, who is describing the lesions, the skin tone of the patient, the virulence of the strain of virus responsible for the disease, and the prevalence of prior smallpox vaccinations.

This will not likely be the last time that a relatively remote disease, such as monkeypox, presents in the United States in a less than classic fashion. Although a ban was subsequently placed on the importation and transportation of African rodents,³⁰ the current world movement of human beings and cargo assures that new infectious agents will continue to journey around the globe with increasing velocity.

REFERENCES

1. Feinberg HM, Solodow JB. Out of Africa. *J Afr Hist* 2002;43:255-61.
2. Frey SE, Belshe RB. Poxvirus zoonoses—putting pocks into context. *N Engl J Med* 2004;350:324-7.
3. Reed KD, Melski JW, Graham MB, Regnery RL, Sotir MJ, Wegner MV, et al. The detection of monkeypox in humans in the western hemisphere. *N Engl J Med* 2004;350:342-50.
4. von Magnus P, Andersen EK, Peterson KB, Birch-Andersen A. A pox-like disease in cynomolgus monkeys. *Acta Pathol Microbiol Scand* 1959;46:156-76.
5. Arita I, Henderson DA. Smallpox and monkeypox in non-human primates. *Bull World Health Organ* 1968;39:277-83.

6. Arita I, Gispén R, Kalter SS, Wah LT, Marennikova SS, Netter R, et al. Outbreaks of monkeypox and serological surveys in nonhuman primates. *Bull World Health Organ* 1972;46:625-31.
7. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. *Bull World Health Organ* 1972;46:593-7.
8. Khodakevich L, Jezek Z, Messinger D. Monkeypox virus: ecology and public health significance. *Bull World Health Organ* 1988;66:747-52.
9. Centers for Disease Control and Prevention. Monkeypox: questions and answers about monkeypox. November 4, 2003. Available from: URL:<http://www.cdc.gov/ncidod/monkeypox/qa.htm>. Accessed July 24, 2004.
10. Centers for Disease Control and Prevention. Monkeypox: report of cases in the United States. Data reported to the CDC as of July 30, 2003. Available from: URL:<http://www.cdc.gov/od/oc/media/mpv/cases.htm>. Accessed March 25, 2006.
11. Centers for Disease Control and Prevention. Monkeypox: embargoed animals and monkeypox virus. December 8, 2003. Available from: URL:www.cdc.gov/ncidod/monkeypox/animals.htm. Accessed March 25, 2006.
12. Arita I, Jezek Z, Khodakevich L, Ruti K. Human monkeypox: a newly emerged orthopoxvirus zoonosis in the tropical rain forests of Africa. *Am J Trop Med Hyg* 1985;34:781-9.
13. Jezek Z, Grab B, Szczeniowski M, Paluku KM, Mutombo M. Clinico-epidemiological features of monkeypox patients with an animal or human source of infection. *Bull World Health Organ* 1988;66:459-64.
14. Jezek Z, Fenner F. Human monkeypox. In: Melnick JL, editor. *Monographs in virology*. Vol 17. Basel: Karger; 1988.
15. Fine PE, Jezek Z, Grab B, Dixon H. The transmission potential of monkeypox virus in human populations. *Int J Epidemiol* 1988;17:643-50.
16. Hammarlund E, Lewis MW, Carter SV, Amanna I, Hansen SG, Strelow LI, et al. Multiple diagnostic techniques identify previously vaccinated individuals with protective immunity against monkeypox. *Nat Med* 2005;11:1005-11.
17. World Health Organization. Technical advisory group of human monkeypox: report of a WHO meeting, January 11-12, 1999. Publication No. WHO/CDS/CSR/APH/99.5. World Health Organization, Geneva, Switzerland. Available from: URL:<http://www.who.int/csr/resources/publications/viral/whocdscsrgraph995.pdf>. Accessed March 25, 2006.
18. Breman JG, Ruti K, Steniowski MV, Zanotto E, Gromyko AI, Arita I. Human monkeypox, 1970-79. *Bull World Health Organ* 1980;58:165-82.
19. Breman JG. Monkeypox: an emerging infection for humans? In: Scheld WM, Craig WA, Hughes JM, editors. *Emerging infections 4*. Washington (DC): ASM Press; 2000. pp. 45-67.
20. Centers for Disease Control and Prevention. Update: multi-state outbreak of monkeypox—Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. *MMWR Morb Mortal Wkly Rep* 2003;52:616-8.
21. Stittelaar KJ, Neyts J, Naesens L, van Amerongen G, van Lavieren RF, Holy A, et al. Antiviral treatment is more effective than smallpox vaccination upon lethal monkeypox virus infection. *Nature* 2006;439:745-8.
22. Huhn GD, Bauer AM, Yorita K, Graham MB, Sejvar J, Likos A, et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. *Clin Infect Dis* 2005;41:1742-51.
23. Sejvar JJ, Chowdary Y, Schomogyi M, Stevens J, Patel J, Karem K, et al. Human monkeypox infection: a family cluster in the midwestern United States. *J Infect Dis* 2004;190:1833-40.
24. Xiao SY, Sbrana E, Watts DM, Siirin M, da Rosa AP, Tesh RB. Experimental infection of prairie dogs with monkeypox virus. *Emerg Infect Dis* 2005;11:539-45.
25. Likos AM, Sammons SA, Olson VA, Frace AM, Li Y, Olsen-Rasmussen M, et al. A tale of two clades: monkeypox viruses. *J Gen Virol* 2005;86:2661-72.
26. Pattyn SR. Monkeypoxvirus infections. *Rev Sci Tech* 2000;19:92-7.
27. Chen N, Li G, Liszewski MK, Atkinson JP, Jahrling PB, Feng Z, et al. Virulence differences between monkeypox virus isolates from West Africa and the Congo basin. *Virology* 2005;340:46-63.
28. Meyer H, Perrichot M, Stemmler M, Emmerich P, Schmitz H, Varaine F, et al. Outbreaks of disease suspected of being due to human monkeypox virus infection in the Democratic Republic of Congo in 2001. *J Clin Microbiol* 2002;40:2919-21.
29. Grabenstein JD, Winkenwerder W Jr. US military smallpox vaccination program experience. *JAMA* 2003;289:3278-82.
30. Rules and regulations. *Federal Register* 2003;68:62353-69. Available from: URL:<http://edocket.access.gpo.gov/2003/03-27557.htm>. Accessed March 26, 2006.

What's new online?

Click on **www.eblue.org** today to find out how you can access back issues of the *Journal of the American Academy of Dermatology* online.